IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	**ABLE0032US.NP**
Inventors:	**Urbaniak et al.**
Serial No.:	**10/563,204**
Filing Date:	**July 10, 2006**
Examiner:	**Szperka, Michael Edward**
Customer No.:	**26259**
Group Art Unit:	**1644**
Confirmation No.:	**6475**
Title:	**Pharmaceutical Compositions comprising an Epitope of Platelet GPIIIA Protein**

Declaration by Mark Peakman, MBBS, BSc, MSc, PhD., FRCPath

I, Mark Peakman hereby declare:

1. I was awarded a BSc in Pharmacology at University College London (First class Honours, 1981); medical degree (MBBS at the same institution, 1984); Masters in Medical Immunology (University of London with Distinction, 1988); PhD in Immunology (University of London, 1993) and Membership of the Royal College of Pathologists (specialization in Clinical Immunology by examination, 1991; awarded Fellowship in 2001). During and after obtaining these degrees I served as junior doctor in house officer positions in London and Bath before specializing in clinical immunology as senior house officer, registrar, senior registrar, lecturer, senior lecturer and reader between 1985 and 2004.

2. I am presently a Professor of Clinical Immunology at King's College in London, England. I am also an Honorary Consultant Immunologist at King's College Hospital. My main research interest is the autoimmune disease Type 1 diabetes. I work on the immune pathogenesis of the disease, and this has led me to try to develop

strategies for treatment and prevention. One approach, which we have taken to Phase 1a clinical trial stage, is that of antigen specific immune therapy using peptide epitopes of islet autoantigens such as proinsulin.

3. I have worked in the area of immunology and vaccine development for 22 years and am therefore very familiar with the type of experiments performed and the experimental data generated indicative of an immunization strategy invoking tolerisation and/or an effective immune response.

4. I have reviewed the above-referenced patent application and the Office communication with a Notification date of March 2, 2010.

5. I believe the patent application provides sufficient experimental data indicative of tolerisation in patients and/or an immunization strategy expected to be effective in preventing or treating conditions such as fetomaternal alloimmune response thrombocytopenia, post-transfusion purpura and platelet refractoriness. This is shown by Figures 3, 5 and 8. The importance of showing that the peptides stimulate PBMCs is that this indicates that in these subjects there is a T cell repertoire available that recognizes the peptides. This fact is essential if the tolerogenic properties of the peptides are to be realized - because the peptide when administered needs to be able to stimulate T cells (e.g. regulatory T cells) to induce tolerance. If the T cell repertoire has been deleted (e.g. in thymic selection) or exhausted (e.g. by peripheral activation) then the therapy cannot work. The PBMC assay is a key assay used in the tolerization field and is widely accepted as indicative of a tolerogenic effect in-vivo. Indeed it is difficult to generate more meaningful data without a clinical trial, and the decision regarding whether to progress to a clinical trial would be based, to a large degree, on the outcome of PBMC assays such as those described in the application.

6. I was provided with copies of the references cited by the Examiner.

The references cited by the Examiner are only a selective part of the picture.

For example, Skyler 2005 describes a therapy that was never intended to be used for tolerance, and so is irrelevant. Indeed this may not be the intended reference.

I am providing another reference by Skyler et al. (2005) which IS relevant and shows a beneficial effect of oral antigen in an autoimmune disease.

Kraus and Mayer refers to IBD, which is not an autoimmune or an alloimmune disease.

This is a developing field and there are some successes, some partial successes and some failures - that is how scientific progress is made. It is true that not every component of this process is worked through yet, but there are many reasons to pursue current goals along the lines described, especially as this type of therapy has an EXCEPTIONAL SAFETY PROFILE, compared with the alternative of immune suppression. Skyler et al. (2005) attached hereto, especially figures 4 and 5, show that a sub-group of subjects at risk of type 1 diabetes and who have high levels of insulin autoantibodies show delayed progression to disease when given daily oral insulin. Further evidence of tolerogenic effects of antigen in Type 1 diabetes come from the effects of GAD65 administration (Ludvigsson) and administration of a proinsulin peptide (Thrower).

The approach is dependent upon having the correct antigen, correct peptide and correct delivery. The clinical trials referred to in Marketletter used myelin (Myloral) and collagen (Collarol) based preparations and were thus very different to the simple, defined peptide antigens, comprising a known polymorphism/epitope, as disclosed in the patent application.

The Examiner cited Dong et al. (1999) for the statement "Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn".

There have been major advances in tolerance assays and the identification of tolerance signatures (see for example back-to-back papers in 2010 June 1st issue of Journal of Clinical Investigation).

Finally, with respect to WO 02/053092, Goodnow (2001) and Bell (2008), these are opinions but to do not detract from the examples of tolerance induction in a complex autoimmune disease using oral insulin and GAD65 provided above. In addition, there have been notable successes in the field of allergy and liver transplantation.

7. In response to the Examiner's discussion of "tolerance" and its meaning, the best definition of tolerance is an operational one, since deletion of T cells,

cytokine production, antibodies etc. can all be viewed as "good" or "bad" (and also tolerant and/or effector responses) depending on context. So, the definition of immunological tolerance that should be used and that includes the concept of operational tolerance is that the subject in question "does not mount an immune response that is damaging to health despite having the capability to do so". This is what the person skilled in the art would understand is meant by the statement in the patent application regarding there being "no effector immune response" associated with tolerance. If this type of operational tolerance is associated with, and reliant upon IgG4 class antibodies (as some tolerance to allergens appears to be) then this is a tolerant response, not an effector one.

8. The literature provides guidance for dosing regimes e.g. the Larche work that is cited suggests 1-10 mcg, as does the Thrower work (attached).

9. I was requested to comment upon the "reasonableness" of the Examiner's argument in the paragraph transitioning pages 7-8 of the Office Action - namely that the patient of the instant method has an underlying genetic susceptibility in that he/she has the wrong GPIIa allele as compared to the administered blood product. This is a nonsensical argument. You could make the same statement about all HLA genes being predisposing to graft rejection disease because when you have a transplanted organ it is rejected as a result of recognition of foreign HLA. The fact is that the human collective genome is full of polymorphisms that can lead to immune recognition - this does not make them predisposing to disease in the sense that most people would appreciate.

10. I was also requested to comment on the Examiner's statement that the diseases he cited are very diverse and are very different from one another thus supporting the argument that problems with tolerization are universally applicable to all disease states.

As I have pointed out already, there are some indications of success. It is a matter of refining the approaches. The problem of tolerization is not always insurmountable, there have been notable successes, for example, in the field of allergy and in renal transplantation, see, for example: -

Identification of a B cell signature associated with renal transplant tolerance in humans.

Newell KA, Asare A, Kirk AD, Gisler TD, Bourcier K, Suthanthiran M, Burlingham WJ, Marks WH, Sanz I, Lechler RI, Hernandez-Fuentes MP, Turka LA, Seyfert-Margolis VL; Immune Tolerance Network ST507 Study Group.

J Clin Invest. 2010 Jun 1;120(6):1836-47.

Peptide immunotherapy in allergic asthma generates IL-10-dependent immunological tolerance associated with linked epitope suppression.

Campbell JD, Buckland KF, McMillan SJ, Kearley J, Oldfield WL, Stern LJ, Grönlund H, van Hage M, Reynolds CJ, Boyton RJ, Cobbold SP, Kay AB, Altmann DM, Lloyd CM, Larché M.

J Exp Med. 2009 Jul 6;206(7):1535-47.

In addition to the work cited above (Thrower, Skyler, Ludvigsson, all post-2003) there is also the work of Salvo Albani in arthritis: Tolerogenic immune responses to novel T-cell epitopes from heat-shock protein 60 in juvenile idiopathic arthritis. Kamphuis S, Kuis W, de Jager W, Teklenburg G, Massa M, Gordon G, Boerhof M, Rijkers GT, Uiterwaal CS, Otten HG, Sette A, Albani S, Prakken BJ. Lancet. 2005 Jul 2-8;366(9479):50-6

11. I was also requested to comment on prior arguments by Applicant that autoimmune diseases are more complicated than the instant claimed methods wherein the antigen is singular allowing for efficient elucidation of relevant T cell epitopes and the Examiner's response that the identities of the multiple autoantigens and the T cell epitopes of autoimmune diseases have been elucidated, allowing for their use in animal models whose encouraging success led to human clinical trials which then failed.

It is probable that choosing the correct antigen and the correct epitope is important. In that sense the applicant is correct in making the case that the fact that the instant disease has a single antigen provides an expectation of success that is greater than that for diseases associated with multiple and/or undefined antigens

12. With respect to the Examiner's concern that data relating to recognition of epitopes by regulatory T cells

has not been provided, I do not think data showing regulatory responses is required. These are clearly going to be potentially lacking in the disease state, and therefore difficult to demonstrate. Although effector and regulatory T cells can see the same epitope, it does not follow that they must. The data on this is often derived from T cell receptor transgenic models in which the T cells only have one specificity to work with, and therefore effectors and regulators must recognize the same epitope.

13. Further, with respect to the Examiner's concern that elaboration of additional antibodies through an IgG response would be counterproductive, induction of IgG4 is definitely associated with successful induction of immune regulation and operational tolerance in the setting of allergy - no reason to suppose it would not be relevant here.

14. Finally, I was asked to address the Examiner's comments at page 10-11 of the Office Action that the specification only teaches linear peptide fragments of 15 mer. Specifically, I was asked after reading the patent application would I understand that the 15 mer peptides are examples of what can be used and that linear peptides of alternative lengths could also be used.

I would know that you take lengths of 15-mer peptides in your initial experiments that include regions of interest, in this case the polymorphism (antithetical allele). This is a question of scale, cost and expediency. Having found these, you would focus down and design a range of peptides for testing that have different N- and C-terminal extensions. Thus it is simply a matter of routine experiments to identify further useful peptides comprising the polymorphism (antithetical allele), as set out in the patent application. The reason for doing this is that it is well known in the field that the nature and length of N- and C- terminal flanking regions of a peptide can have profound effects on its ability to function in interactions with T cells. For example see:

T cell receptor recognition of MHC class II-bound peptide flanking residues enhances immunogenicity and results in altered TCR V region usage.
Carson RT, Vignali KM, Woodland DL, Vignali DA.
Immunity. 1997 Sep;7(3):387-99.

Amino acid residues that flank core peptide epitopes and the extracellular domains of CD4 modulate differential signaling through the T cell receptor.
Vignali DA, Strominger JL.
J Exp Med. 1994 Jun 1;179(6):1945-56.

I hereby declare that all statements herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

M. Peakman

Mark Peakman

2/7/10

Date